US04/38490

THE PATENTS ACT, 1970

REC'D 07 JAN 2005
WIPO PCT

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification & Abstract of the extract of Patent Application No.370/CHE/2004, dated 22/04/2004 by Dr. Reddy's Laboratories Ltd., an Indian Company registered under the Indian Companies Act, 1956, having its registered office at 7-1-27 Ameerpet, Hyderabad, Andhra Pradesh, India, 500 016.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 8th day of November 2004

M.S. Venkataraman

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PAT[redacted]FFICE BRANCH
GOV[redacted]ENT OF INDIA
Guna[redacted], 6th Floor, Annex.II
No.443, Anna Salai, Teynampet, Chennai – 600 018

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

BEST AVAILABLE COPY

ORIGINAL

22 APR 2004 370 /CHE/2004

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(Section 5(2), 7, 54 and 135 and Rule 33A)

I/We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare –that

1. (a) I am/ we are in possession of an invention titled "Novel process for the preparation of (+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (Escitalopram) and pharmaceutically acceptable salts thereof"

   (b) that the complete specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to me/us.

2. Further declare that the inventor(s) for the said invention are **Sundaram Venkataraman, Mathad Vijayavitthal Thippannachar, Vankawala Pravinchandra Jayantilal, Ghanta Mahesh Reddy, Elati Ravi Rama Chandrashekar, Kolla Naveen Kumar, Govindan Shanmugam, Madhavi Maddipatla, Chalamala Subrahmanyeswara Rao and Vajrala Venkata Reddy.** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**

3. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows.

4. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/We are the applicant / patentee

5. We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on _____ under section 16 of the Act.

6. That We are the assignee or legal representative of the true and first inventors.

7. That our address for service in India is as follows:

S. Venkataraman

Sundaram Venkataraman
Vice President-R&D
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P.- 500 016

8. Following declaration was given by the inventor(s) or applicant(s) in the convention country:

9. We, the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative

(Signed) S. Venkataraman

Sundaram Venkataraman
Plot No. 141, Flat No. 202,
Sharda Nilayam,
Mohiti Nagar,
Hyderabad-500 018.

(Signed)

Mathad Vijayavitthal Thippannachar
Flat No 114, Adithya Homes
Adithya Nagar, Opp: JNTU
Pragathi Nagar Road, KPHB
Hyderabad-500 072

(Signed) V N Jawalawala

Vankawala Pravinchandra Jayantilal
Flat No. 105, Vishwanath Arcade
Bhagya Nagar,
Hyderabad – 500 072

(Signed)_____

Madhavi Maddipatla
LIGB 393,
Dr. A.S. Rao Nagar,
Hyderabad – 500 062

(Signed)_____

Chalamala Subrahmanyeswara Rao
Plot No 27, Road No. 9
Vivekanand Nagar Colony
Kukatapally
Hyderabad – 500 072

(Signed)_____

Vajrala Venkata Reddy
EWS - 1172/A,
Road No. 5,
KPHB Colony,
Hyderabad – 500 072

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachments with the application
(a) Complete specification (--80--- pages, in triplicate)
(b) Drawings (------- pages, in triplicate)

(Signed) _____

Ghanta Mahesh Reddy
Flat No. 408, Shruti Block,
ROIS developer,
Miyapur,
Hyderabad – 500 050

(Signed) _____

Elati Ravi Rama Chandrashekar
H No. ER-5
Jalavayu Vihar
KPHB colony
Hyderabad- 500 072

(Signed) _____

Kolla Naveen Kumar
H. No. 313,
Jalavayu Vihar
KPHB colony
Hyderabad- 500 072

(Signed) _____

Govindan Shanmugam
MIG 79
Bharat Nagar colony
Hyderabad -500018

(c) Priority documents(s)

(d) Statement and Undertaking on Form-3.

(e) Power of authority

(f) Abstract of the invention (---01--- page, in triplicate)

(g) Fee Rs. 3000.00 (three thousand rupees only) in cheque bearing No. 341353 dated 16th April 2004 drawn on HDFC Bank Limited, Lakdi-kapul, Hyderabad -4.

We request that a patent may be granted to me/us for the said invention.

Dated this 13th day of April 2004.

(Signed) S. Venkataraman

Sundaram Venkataraman
Vice president (R&D),
Dr. Reddy's Laboratories Limited.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

Received Rs ... in Cash
Cheque/D.D./P.O./B.D. No. ...
Vide C.B.R. No. ...
2214

FORM-2

THE PATENTS ACT, 1970

ORIGINAL

2 APR 2004 576 /CHE/2004

COMPLETE SPECIFICATION

(Section-10)

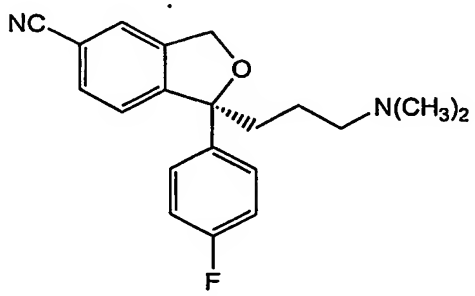
A novel process for the preparation of (+)-1-(3-dimethylaminopropyl)-1-(4-flourophenyl)-1,3-dihydrobenzofuran-5-carbonitrile (Escitalopram) and pharmaceutically acceptable salts thereof

Dr. Reddy's Laboratories limited,
An Indian company having its registered office at 7-1-27, ameerpet,
Hyderabad-500016, A.P., India.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

FIELD OF INVENTION:

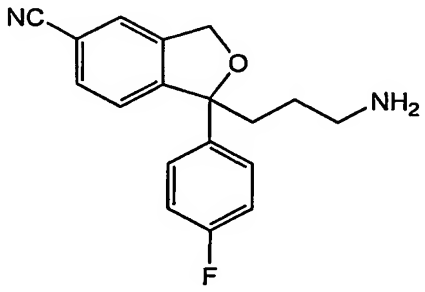
The present invention relates to a novel process for the preparation of escitalopram, which is chemically known as (+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3–dihydroisobenzofuran–5–carbonitrile represented by Formula- (I)



Formula-I

Escitalopram is a well-known antidepressant drug, and is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-*HT*) reuptake inhibitor, accordingly having antidepressant activities.

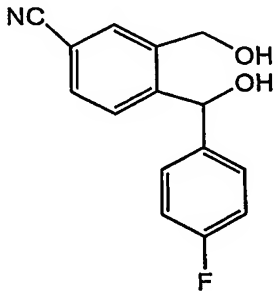
The main object of the present invention is the novel process for the preparation of escitalopram which comprises, process for the preparation of didesmethyl citalopram of Formula-II, which is a useful intermediate in the preparation of escitalopram of Formula (I). And dynamic resolution of Formula (II) followed by methylation to get the escitalopram of Formula (I)



Formula-II

BACKGROUND OF INVENTION:

Escitalopram was first disclosed in **US patent No 4,943,590** corresponding to **EP-B1-347066.** This patent describes two processes for the preparation of Escitalopram (S-enantiomer of citalopram). Both the processes utilize the racemic diol having the formula (III) as a starting material

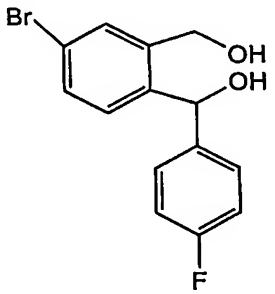


Formula - III

According to the first process, the diol of the formula (III) is reacted with an enantiomerically pure acid derivative, such as (+) or (-)-∝-methoxy-∝-triflouromethyl-phenylacetyl chloride to form a mixture of diastereomeric esters, which are separated by HPLC or fractional crystallization, where upon the ester with the correct stereochemistry, is converted into escitalopram by cyclization. According to the second process, the diol of formula (III) is separated by treating with an enantiomerically pure acid such as (+)-di-*p*-tolulyltartaric acid followed by separating the required isomer by crystallization. Which upon cyclization yields escitalopram of Formula (I). Both routes found to be economically and environmentally infeasible due to their low yields.

WO03/006449 discloses a process for the preparation of escitalopram of Formula (I), which involves chromatographic separation of the enantiomers of citalopram and intermediate using a chiral stationary phase. Which is industrially not feasible and not economic.

W0 03/087081 describes a process for the preparation of escitalopram via the (4-bromo-2-(hydroxymethyl) phenyl)-(4-flouro phenyl) methanol of Formula (IV), in which the racemic diol is converted to an enantiomerically enriched form by first converting the diol into monoester intermediate and then reacting monoester intermediate with an optically active acid to form a diastereomeric salt. The salt is then crystallized to obtain enantiomerically enriched S-isomer where upon the monoester intermediate is further converted to escitalopram through suitable chemical conversions. The major drawbacks of the described process are, low yields, and usage of hazardous materials like copper cyanide and lengthy process of production



Formula (IV)

WO 03/051861 A1 describes the separation of racemic Br-citalopram to the corresponding S-Br-citalopram by fractional crystallization of diastereomeric salt of Br-citalopram and followed by hydrolysis and cyanation to get the Escitalopram. The major draw back of this process is the use of copper cyanide in presence of palladium or nickel catalyst for the conversion of bromo to cyano group, which is industrially not feasible and safe to handle. This patent also describes

the separation of bromodiol intermediate by chromatography using chiral stationary phase, which is industrially not feasible to practice at the plant level, which involves the hazardous chemical for the conversion of bromo to cyano group as described above.

Recent patent application **W02004/014821A1** describes process for the preparation of escitalopram of compound of Formula-I, which involves the enzymatic conversions, and generally enzyme reactions are not suitable for the industrial productions and also expensive.

With this background, we felt a need for cost effective, safe and industrially feasible route to synthesize the Escitalopram of formula-I and invention made towards this goal is described here.

It is note worthy to mention that, the prior art processes teaches that there are no other methods available, where the S-citalopram compound of Formula-I is prepared in a high yield with high chiral purity.

Eur. J. Med. Chem. **(1977) 12, 289,** first time discloses the didesmethylcitalopram of Formula-II, but the process is not described in the article.

OBJECTIVE OF INVENTION:

Objective of the present invention is to develop a novel process for the production of (+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3–dihydroisobenzofuran–5–carbonitrile of Formula (I) and its corresponding isomer (-)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3–dihydroisobenzofuran–5–carbonitrile of Formula (V),

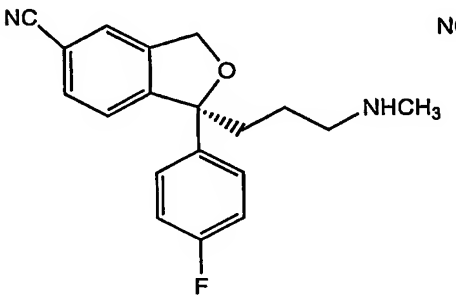
Another objective of the present invention is to develop the plant friendly and economic process for preparation of compound of Formula-II with high yield and purity.

The major objectives of the present invention is to provide the first time industrially feasible and cost economic process for the resolution of racemic 1-(3-amino propyl)-1-(4-

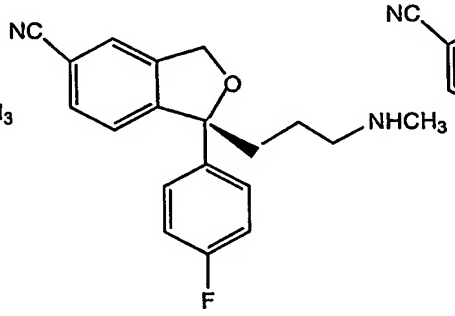
fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile of Formula (II) to yield the required enantiomers in a pure form which can be further methylated to get the S-citalopram of compound of Formula (I) and R-citalopram of compound of Formula (V) correspondingly.

The objective of the present invention is also to provide an improved, industrially feasible and cost effective process for the preparation of racemic citalopram of compound of Formula (VIII)

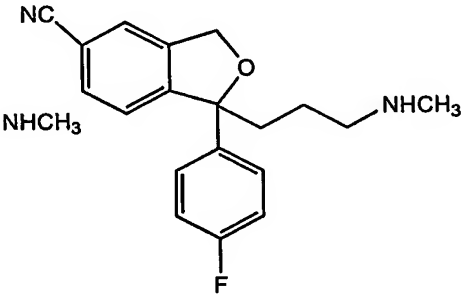
Present invention also provides the suitable and industrially feasible process for the preparation of (+)-desmethyl citalopram of Formula (IX), (-) –desmethyl citalopram of Formula (X), and racemic desmethyl citalopram of Formula (XIII), and



Formula -IX



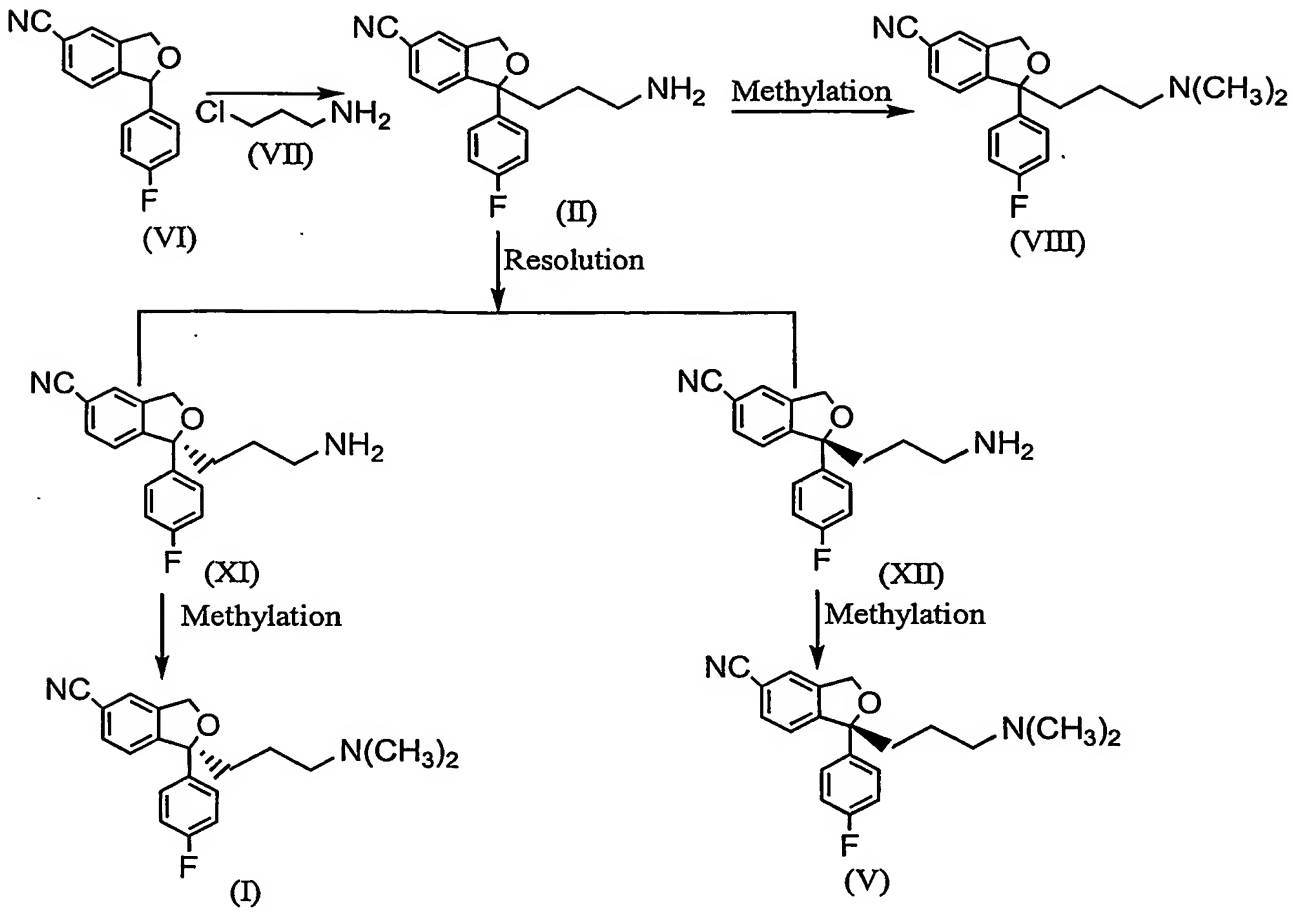
Formula -X



Formula -XIII

SUMMARY OF INVENTION:

The present invention provides novel process for the production of (+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3–dihydroisobenzofuran–5– carbonitrile of Formula (I) which involves condensation of isobenzofuran of Formula (VI) with chloropropyl amine of Formula (VII) to afford a compound of Formula (II), which is further subjected to resolution followed by methylation to afford compound of Formula-I as mentioned in Scheme -I.

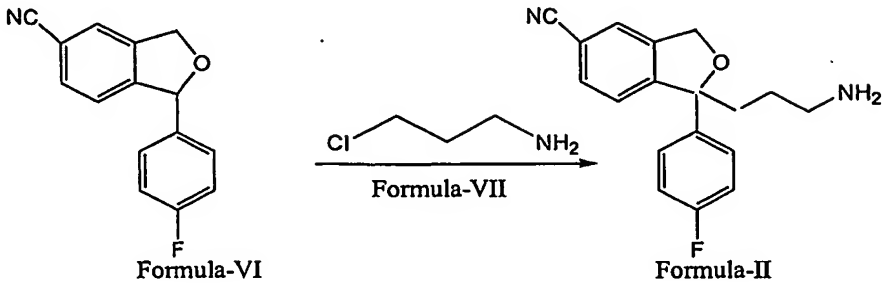


Scheme-I

According to the present invention the compound of Formula-I can be synthesized in a good yield and purity with industrially feasible, cost effective and safe manner.

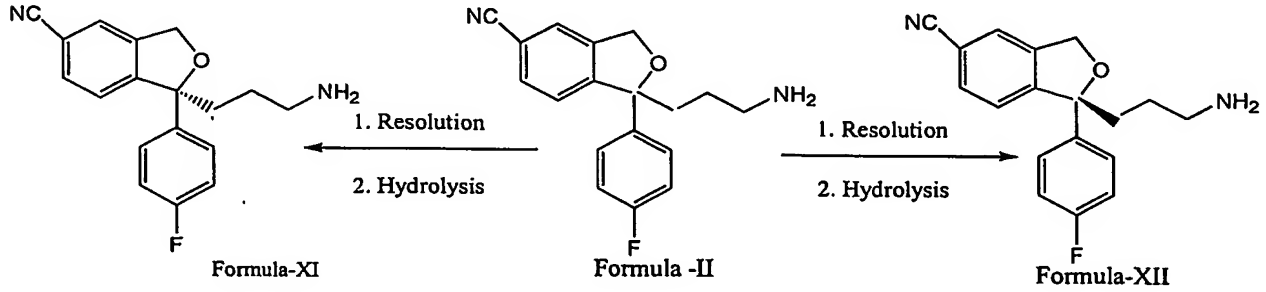
The present invention provides the novel process for the production of racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile of Formula (II) by condensation of isobenzofuran of Formula (VI) with chloropropyl amine of Formula (VII) in a

good yield and purity with industrially feasible, cost effective and safe manner as described here in Scheme-II



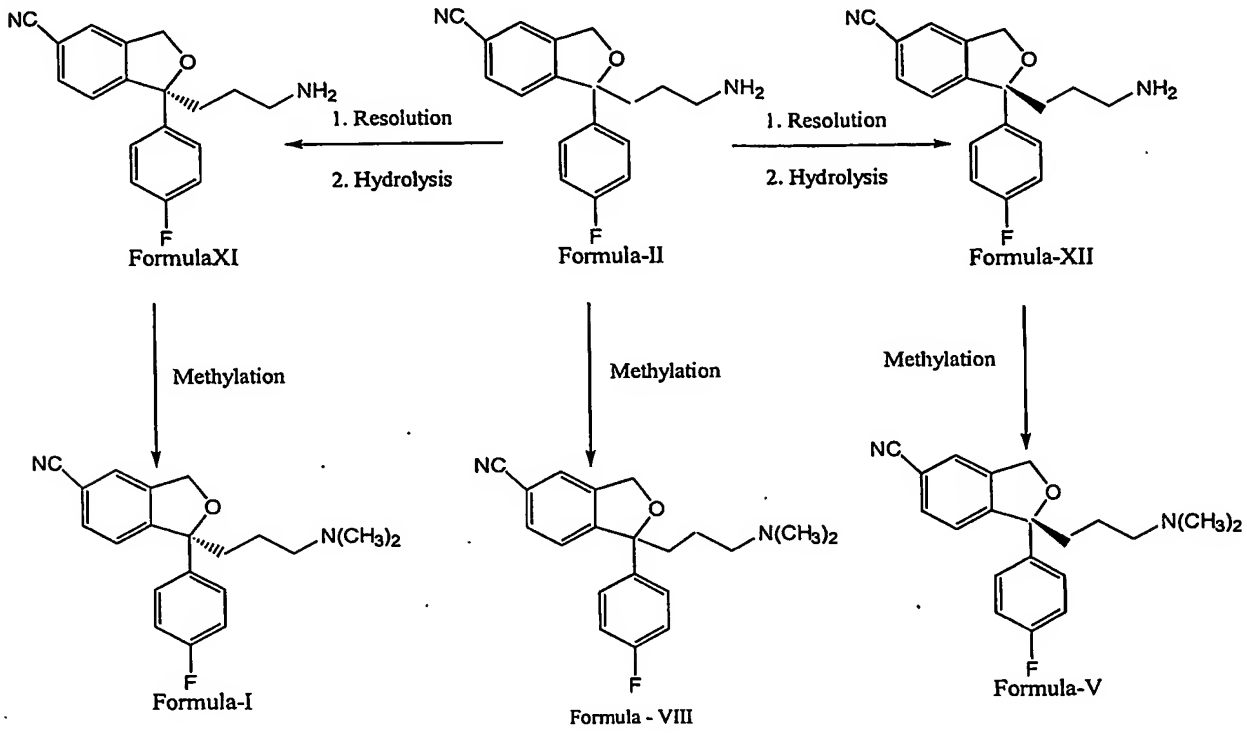
Scheme-II

The present invention also provides the novel process for the preparation of Escitalopram of Formula (I) through the resolution of the racemic 1-(3-amino propyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile of Formula (II) to its corresponding (+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile of Formula (XI) and (-)-1-(3-amino propyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile of Formula (XII) through the dynamic diastereoisomeric salt formation of the amine of the Formula (II) with chiral acids followed by their hydrolysis as shown in the below Scheme-III



Scheme-III

The present invention also provides the process for the preparation of S-citalopram of Formula-I and R-citalopram of Formula-V by methylation of the compounds of Formula (XI) and Formula (XII) respectively as mentioned in Scheme-IV



Scheme-IV

The present invention also provides the process for the preparation of citalopram of Formula – (VIII) by methylation of compound Formula –(II) in a high yield and purity as shown in Scheme – IV

Escitalopram can also be prepared from citalopram by diastereomeric salt formation followed by separation and hydrolysis.

The present invention also relates to a novel process for the preparation of Escitalopram and /or its any salts from racemic citalopram base or its salts. The process for the preparation of Escitalopram and its pharmaceutically acceptable salts of present invention comprises reaction of racemic citalopram (VIII) with an enantiomerically enriched acid HY*, where Y* is chiral group to form diastereomeric salt of (VIII) having Y* as counter ion, which was crystallized to separate the required salt of escitalopram which on further hydrolysis afford the Escitalopram of Formula (I).

DETAILED DESCRIPTION OF INVENTION:

According to the present invention, the process for the preparation of (+) 1-[3–(N, N'-dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro–5–isobenzo furancarbonitrile (S-citalopram) of the Formula–I comprising the alkylation of 5-cyano-1-(4-fluro phenyl)-1,3-dihydro isobenzofuran of Formula-VI with a compound of formula-VII in a suitable base and solvent as described, to afford racemic 1-(3-amino propyl)-1-(4-flouro phenyl)-1,3 dihydro-5-isobenzofurancarbonitrileof Formula-II. Which is further subjected to resolution with a suitable chiral acid in a suitable solvent system to obtain diastereomeric salt of the amine of Formula (II). Hydrolysis of the obtained diastereomeric salts followed by methylation of S- amine of the compound of Formula (XI) or optionally Formula (XII) to afford S-citalopram of Formula (I) or R-citalopram of Formula (V).

a) According to the present invention a novel process for the preparation of didesmethylcitalopram of Formula-II comprises;

1. heating a solution of a base selected form, LDA (lithium diisopropyl amine), NaH, n-BuLi, and metal oxides; such as NaOMe, KOMe, LiOMe, NaOtBu, KOtBu and LiOtBu preferably NaH, or KtBuO or LDA, more preferably in KtBuO in a aprotic solvent

selected from the list of DMSO, THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers; such as diethyl ether, methyl tert.butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, in a anhydrous condition under nitrogen atmosphere, at a temperature of 50 – 120°C; preferably 60-65°C for more than a hour

2. cooling the reaction mixture of step (1) to temperature of 10-50°C, preferably to a temperature of 30-35°C
3. dissolving 5-cyano-1- (4-fluoro phenyl)-1,3-dihydrobenzofuran of formula-VI in a suitable aprotic solvent selected from the list of dimethyl sulfoxide (DMSO), THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, followed by it's addition to the reaction mixture of step (2) at ambient temperature;
4. stirring the reaction mass of step (3) for a period of 10 – 60 minutes, preferably for a period of 10-15 minutes
5. dissolving the chloropropyl amine of formula-VII in a aprotic solvent selected from the list of dimethyl sulfoxide (DMSO), THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons

such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, followed by addition to the reaction mixture of step (4) at ambient temperature:

6. heating the reaction mass of step (5) to a temperature of 40 – 140°C for a period of 1 to 6 hrs; preferably a temperature of 40 – 45°C for 1 to 1.5 hrs
7. quenching of the reaction mass of step (6) using ice- cold water at a temperature of – 5 to 25 °C, preferably at a temperature of 0 to 5°C
8. extraction of the compound from reaction mass of step (7) with an organic solvent selected from the list of dichloromethane, chloroform, dichloroethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether, preferably toluene
9. distilling off the solvent under reduced pressure from the reaction solution of step (8) to get the residue
10. suspending the residue of step (9) in water followed by adjusting pH of the solution between 2 and 6 with a solution comprising hydrochloric acid, acetic acid, sulphuric acid; preferably hydrochloric acid solution followed by washing solution with a suitable organic solvent selected from class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably toluene
11. basifying the aqueous solution of step (10) to a pH of 8 to 13 with a basic solution comprising of a base such as sodium hydroxide, sodium carbonate sodium bicarbonate,

potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution

12. extracting the compound from the basified aqueous layer of step (11) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene
13. distilling the solvent from the reaction solution of step (12) to obtain a didesmethylcitalopram of compound of Formula (II) in the form of thick syrup.
14. didesmethylcitalopram of compound of Formula (II) of step (13) optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of formula (II)
15. hydrolysis of the dried or wet salt of formula (II) of the step (14) in water with suitable alkaline solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution
16. extracting the compound of formula (II) from the solution of step (15) in a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene,

ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene

17. distilling the organic solvent of step (16) to afford the compound of Formula (II) with satisfactory yield and purity

(b) According to the present invention a novel process for the preparation of Escitalopram of Formula-I comprises;

(i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of Formula (II) in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile;

(ii) stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes;

(iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 –camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (-) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol,

butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures;

(iv) addition of the reaction mass of step (iii) to a reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes;

(v) heating the reaction mass of step (iv) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45to 60 minutes;

(vi) cooling the reaction mass of step (v) to a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours;

(vii) filtering the obtained solid in step (vi) followed by washing with a solvent used in step (iii);

(viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a diastereomeric salt of compound of Formula (II);

(ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes,

xylene or alkanes and mixture thereof; preferably in a mixture of 15:1 acetonitrile and water combination;

(x) heating the reaction mass of step (ix) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes;

(xi) cooling the reaction mass of step (x) to a temperature of –20 to +30°C for a period of 1 to 72 hours; preferably –5 to 5°C for 1 to 3 hours;

(xii) filtering the obtained solid in step (xi) followed by washing with a solvent used in step (ix) ;

(xiii) drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford (+)-1- (3- aminopropyl)-1-(4 –fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of (-) DPTTA salt of compound of Formula (XI);

(xiv) suspending the solid obtained in step (xiii) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xv) extracting the compound of formula -XI from the basified aqueous layer of step (xiv) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvi) distilling the solvent from the reaction solution of step (xv) to obtain (+) didesmethylcitalopram of compound of Formula (XI) with satisfactory yield and purity;

(xvii) reacting the compound formula (XI) in step (xvi) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours, more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours;

(xviii) cooling the reaction mass of step (xvii) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid;

(xix) distilling the reaction solution of step (xviii) to obtain a thick residue;

(xx) suspending the residue of step (xix) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide;

(xxi) extracting the compound from the basified aqueous layer of step (xx) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether;

(xxii) distilling the solvent from the reaction solution of step (xxi) to afford (+)-1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 – isobenzofurancarbonitrile of the Formula – I.

© According to the present invention a novel process for the preparation of R-citalopram of formula-V comprises;

i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of Formula (II) in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile;

ii) stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes;

iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 – camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (+) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane,

dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures;

(iv) addition of reaction mass of step (iii) to reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes;

(v) Heating the reaction mass of step (iv) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45to 60 minutes;

(vi) Cooling the reaction mass of step (v) to a temperature of –20 to 40°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours;

(vii) filtering the obtained solid in step (vi) followed by its washing with a solvent used in step (ii);

(viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford diastereomeric salt of compound of Formula (II);

(ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures;

(x) heating the reaction mass of step (ix) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably 60 –65°C for 45 to 60 minutes;

(xi) cooling the reaction mass of step (x) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours;

(xii) filtering the obtained solid in step (xi) followed by its washing with a solvent used in step (ix);

(xiii) drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (-)-1- (3-aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of (+) DPTTA salt of compound of Formula (XII);

(xiv) suspending the solid obtained in step (xiii) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xv) extracting the compound from the basifying aqueous layer of step (xiv) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvi) distilling the solvent from the reaction solution of step (xv) to obtain (-) didesmethylcitalopram of compound of Formula (XII) with satisfactory yield and purity;

(xvii) reacting the compound formula (XII) in step (xvi) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with

formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours, more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours;

(xviii) cooling the reaction mass of step (xvii) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid;

(xix) distilling the reaction solution of step (xviii) to obtain a thick residue;

(xx) suspending the residue of step (xix) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide;

(xxi) extracting the compound from the basified aqueous layer of step (xx) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether;

(xxii) distilling the solvent from the reaction solution of step (xxi) to afford (-)-1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 – isobenzofurancarbonitrile of the formula – V;

(d) According to the present invention a novel process for the preparation of citalopram of formula-VIII comprises;

(i) heating a solution of a base selected form, LDA (lithium diisopropyl amine), NaH, n-BuLi, and metal oxides; such as NaOMe, KOMe, LiOMe, NaOtBu, KOtBu and LiOtBu preferably NaH, or KtBuO or LDA, more preferably in KtBuO in a aprotic solvent selected from the list of DMSO, THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers; such as diethyl ether, methyl

tert.butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, in a anhydrous condition under nitrogen atmosphere, at a temperature of 50 – 120°C; preferably 60-65°C for more than a hour;

(ii) cooling the reaction mixture of step (i) to temperature of 10-50°c, preferably to a temperature of 30-35°C;

(iii) dissolving 5-cyano-1- (4-fluoro phenyl)-1,3-dihydrobenzofuran of formula-V in a suitable aprotic solvent selected from the list of dimethyl sulfoxide (DMSO), THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, followed by it's addition to the reaction mixture of step (ii) at ambient temperature;

(iv) stirring the reaction mass of step (iii) for a period of 10 – 60 minutes, preferably for a period of 10-15 minutes;

(v) dissolving the chloropropyl amine of formula-VI in a aprotic solvent selected from the list of dimethyl sulfoxide (DMSO), THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons such as toluene, benzene, cyclohexane or alkanes and mixtures there

of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, followed by it's addition to the reaction mixture of step (63) at ambient temperature;

(vi) heating the reaction mass of step (v) to a temperature of 40 – 140°C for a period of 1 to 6 hrs; preferably a temperature of 40 – 45°C for 1 to 1.5 hrs;

(vii) quenching of the reaction mass of step (vi) using ice- cold water at a temperature of – 5 to 25 °C, preferably at a temperature of 0 to 5°C;

(viii) extraction of the compound from reaction mass of step (vii) with an organic solvent selected from the list of dichloromethane, chloroform, dichloroethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether, preferably toluene;

(ix) distilling off the solvent under vacuum from the reaction solution of step (viii) to get the residue;

(x) suspending the residue of step (ix) in water followed by adjusting pH of the solution between 2 and 6 with a solution comprising hydrochloric acid, acetic acid, sulphuric acid; preferably hydrochloric acid solution followed by washing solution with a suitable organic solvent selected from class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably toluene;

(xi) basifying the aqueous solution of step (x) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution

(xii) extracting the compound from the basified aqueous layer of step (xi) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xiii) distilling the solvent from the reaction solution of step (xii) to obtain a didesmethylcitalopram of compound of Formula (II) in the form of thick syrup;

(xiv) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of formula (II);

(xv) hydrolysis of the dried or wet salt of formula (II) of the step (xiv) in water with suitable alkaline solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xvi) extracting the compound of formula (II) from the solution of step (xv) in a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvii) distilling the organic solvent of step (xvi) to afford the compound of formula (II) with satisfactory yield and purity;

(xviii) reacting the compound formula (II) in step (xvii) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours, more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours;

(xix) cooling the reaction mass of step (xviii) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid;

(xx) distilling the reaction solution of step (xix) to obtain a thick residue;

(xxi) suspending the residue of step (xx) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide

(xxii) extracting the compound from the basified aqueous layer of step (xxi) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether;

(xxiii) distilling the solvent from the reaction solution of step (xxii) to afford racemic 1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 – isobenzofurancarbonitrile of the Formula – VIII;

(e) According to the present invention a novel process for the preparation of racemic desmethylcitalopram of Formula-XIII comprises;

(i) dissolving the didesmethyl citalopram of Formula (II) in a solvent selected from the list of solvents ethers; such as diethyl ether, methyl-tert-butyl ether, hydrocarbons;

such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably the solvent is toluene;

(ii) addition of benzaldehyde to reaction mass of step (i) to ambient temperature;

(iii) refluxing the above reaction mass of step (ii) with a water separator for a period of 2 to 10 hours at a temperature of 100-110°C preferably till the last drop of the water was collected;

(iv) reacting the reaction mass of step (iii) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1-1.5 hours

(v) cooling the reaction mass of step (iv) to a temperature of 90-95°C;

(vi) treating the reaction mass of step (v) with water at a temperature at 90-95°C;

(vii) refluxing the reaction mass of step (vi) for a period of 20 –120 minutes at 90-125°C preferably 100-110°C for 30-40 minutes;

(viii) cooling the reaction mass of step (vii) to ambient temperature and followed by washing with a suitable organic solvents selected from the class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether;

(ix) basifying the aqueous solution of step (viii) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH of 12-13;

(x) extracting the compound from the basified aqueous layer of step (ix) with a suitable organic solvents selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether;

(xi) washing the organic layer of step (x) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate;

(xii) distilling the solvent from the reaction solution of step (xi) to obtain a racemic desmethyl citalopram of compound of Formula (XIII) in the form of thick syrup;

(xiii) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols; such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents; such as dichloroethane, dichloromethane, chloroform, esters; such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons; such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of Formula (XIII);

(f) According to the present invention a novel process for the preparation of (+) desmethylcitalopram of Formula-IX comprises;

(i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of Formula (II) in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile;

(ii) stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes;

(iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 –camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (-) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures;

(iv) addition of reaction mass of step (iii) to reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes;

(v) heating the reaction mass of step (iv) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes;

(vi) cooling the reaction mass of step (v) a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours;

(vii) filtering the obtained solid in step (vi) followed by its washing with a solvent used in step (i);

(viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of diastereomeric salt of compound of Formula (II);

(ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures;

(x) heating the reaction mass of step (ix) to a temperature of 40 to 100°C for a period of 1 to 6 hours; preferably a temperature of 60 to 65°C for 45 to 60 minutes;

(xi) cooling the reaction mass of step (x) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours;

(xii) filter the obtained solid in step (xi) followed by its washing with a solvent used in step (ix);

(xiii) drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (+)-1- (3-aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of DPTTA salt of compound of Formula (XI);

(xiv) dissolving the solid obtained in step (xiii) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xv) extracting the compound from the basifying aqueous layer of step (xiv) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvi) distilling the solvent from the reaction solution of step (xv) to obtain a compound of formula (+) didesmethylcitalopram of compound of Formula (XI) with satisfactory yield and purity;

(xvii) dissolving the (+)-didesmethyl citalopram of Formula (XI) in a solvents selected from the list of solvents ethers; such as diethyl ether, methyl-tert-butyl ether, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably the solvent is toluene;

(xviii) addition of benzaldehyde to reaction mass of step (xvii) at ambient temperatures;

(xix) refluxing the above reaction mass of step (xviii) with a water separator for a period of 2 to 10hrs at a temperature of 100-110°C preferably till the last drop of the water was collected;

(xx) reacting the reaction mass of step (xix) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1 to 1.5 hours;

(xxi) cooling the reaction mass of step (xx) to a temperature of 90-95°C;

(xxii) treating the reaction mass of step (xxi) with water at a temperature at 90-95°C;

(xxiii) refluxing the reaction mass of step (xxii) for a period of 20 –120 minutes at 90-125°C preferably 100-110°C for 30-40 minutes;

(xxiv) cooling the reaction mass of step (xxiii) to ambient temperature and followed by washing with a suitable organic solvents selected from the class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether;

(xxv) basifying the aqueous solution of step (xxiv) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH of 12-13;

(xxvi) extracting the compound from the basified aqueous layer of step (xxv) with a suitable organic solvents selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether;

(xxvii) washing the organic layer of step (xxvi) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate;

(xxviii) distilling the solvent from the reaction solution of step (xxvii) to obtain a (+)-desmethyl citalopram of compound of Formula (IX) in the form of thick syrup;

(xxix) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of formula (IX);

(g) According to the present invention a novel process for the preparation of (-) - desmethylcitalopram of formula-X comprises;

(i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of Formula (II) in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile;

(ii) stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes;

(iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 –camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (+) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures;

(iv) addition of reaction mass of step (iii) to reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes;

(v) heating the reaction mass of step (iv) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45to 60 minutes;

(vi) cooling the reaction mass of step (v) a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours;

(vii) Filter the obtained solid in step (vi) followed by its washing with a solvent used in step (i);

(viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 to 65°C for 6 to 8 hours to afford a diastereomeric salt of compound of Formula (II);

(ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures;

(x) heating the reaction mass of step (ix) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45to 60 minutes;

(xi) cooling the reaction mass of step (x) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours;

(xii) filter the obtained solid in step (xi) followed by its washing with a solvent used in step (ix);

(xiii) drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (-)-1- (3-aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of DPTTA salt of compound of Formula (XII);

(xiv) dissolving the solid obtained in step (139) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate

or potassium bicarbonate; preferably using sodium hydroxide solution preferably 12-13;

(xv) extracting the compound from the basifying aqueous layer of step (140) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvi) distilling the solvent from the reaction solution of step (xv) to obtain a compound of formula (-) didesmethylcitalopram of compound of Formula (XII) with satisfactory yield and purity;

(xvii) dissolving the (-)-didesmethyl citalopram of Formula (XII) in a solvents selected from the list of solvents ethers; such as diethyl ether, methyl-tert-butyl ether, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably the solvent is toluene;

(xviii) addition of benzaldehyde to reaction mass of step (xvii) at ambient temperature;

(xix) refluxing the above reaction mass of step (xviii) with a water separator for a period of 2 to 10 hours at a temperature of 100-110°C preferably till the last drop of the water was collected;

(xx) reacting the reaction mass of step (xix) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1-1.5 hours;

(xxi) cooling the reaction mass of step (xx) to a temperature of 90-95°C;

(xxii) treating the reaction mass of step (xxi) with water at a temperature at 90-95°C;

(xxiii) refluxing the reaction mass of step (xxii) for a period of 20 to120 minutes at 90 to125°C preferably 100-110°C for 30-40 minutes;

(xxiv) cooling the reaction mass of step (xxiii) to ambient temperature and followed by washing with a suitable organic solvents selected from the class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether;

(xxv) basifying the aqueous solution of step (xxiv) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH of 12-13;

(xxvi) extracting the compound from the basified aqueous layer of step (xxv) with a suitable organic solvents selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether;

(xxvii) washing the organic layer of step- (xxvi) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate;

(xxviii) distilling the solvent from the reaction solution of step (xxvii) to obtain a (-)-desmethyl citalopram of compound of Formula (X) in the form of thick syrup;

(xxix) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as

acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of formula (X);

Example-1

Preparation of 1- (3- aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile (Formula-II)

A potassium salt of DMSO was prepared by adding 7.5 gm of potassium tertiary butoxide in DMSO (40 ml) at 60-65°C under nitrogen atmosphere. To the resulting solution a solution of 1-(4-fluorophenyl)-1,3-dihydroiso benzofuran-5-carbonitrile (10gm) in DMSO (35 ml) was added within 10 minutes at 25 –30 °C. After maintaining for 15-20 minutes, a solution of 3-chloropropyl amine (12gm) in DMSO (2.5ml) was added at once at the temperature between 25-30°C. After the addition is over, reaction mixture was heated slowly to 40-45°C for 60 to 70 minutes. The reaction mixture is then quenched with ice-cold water (200 ml) and extracted with toluene (100 ml). Aq. Layer was again extracted with (3 x 100 ml) of toluene. Toluene layer was dried over anhydrous sodium sulphate and distilled off under vacuum below 65°C to get thick syrup. Then resulting residue was suspended in 50 ml water and acidified to a pH 2-3 with 10% aqueous Hydrochloric acid solution. The resulting acidic solution was then washed with (4 x 100 ml) of toluene. The aq layer was basified with 10% aqueous sodium hydroxide solution to pH 10-11and extracted with (3 x 100 ml) of toluene. The combined toluene layer was washed with water (2 x 100 ml), followed by distillation of toluene layer to afford the compound of the formula (V) as wine red syrup (10 gm).

Example-2 (In Acetone)

Preparation of 1- (3- aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile (Formula-II)

A potassium salt of DMSO was prepared by adding 7.5 gm of potassium tertiary butoxide in acetone (40 ml) at 60-65°C under nitrogen atmosphere. To the resulting solution a solution of 1-(4-fluorophenyl)-1,3-dihydroiso benzofuran-5-carbonitrile (10gm) in acetone (35 ml) was added within 10 minutes at 25 –30 °C. After maintaining for 15-20 minutes, a solution of 3-chloropropyl amine (12 gm) in acetone (2.5ml) was added at once at the temperature between 25-30°C. After the addition is over, reaction mixture was heated slowly to 40-45°C for 60 to 70 minutes. The reaction mixture is then quenched with ice-cold water (200 ml) and extracted with toluene (100 ml). Aq. Layer was again extracted with (3 x 100 ml) of toluene. Toluene layer was dried over anhydrous sodium sulphate and distilled off under vacuum below 65°C to get thick syrup. Then resulting residue was suspended in 50 ml water and acidified to a pH 2-3 with 10% aqueous Hydrochloric acid solution. The resulting acidic solution was then washed with (4 x 100 ml) of toluene. The aqueous layer was basified with 10% aqueous sodium hydroxide solution to pH 10-11and extracted with (3 x 100 ml) of toluene. The combined toluene layer was washed with water (2 x 100 ml), followed by distillation of toluene layer to afford the compound of the formula (V) as wine red syrup (8 gm).

Example-3

Preparation of (+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3–dihydroiso benzofuran – 5 – carbonitrile: (Formula-XI)

1-(3- aminopropyl)-1-(4 -fluorophenyl)-1,3 dihydroisobenzofuran – 5 – carbonitrile (10 gm) was dissolved in 50 ml of acetonitrile. A solution of (-)-di-p-tolyltartaric acid (13 gm in 20 ml of acetonitrile) was added slowly at ambient temperature. The reaction mixture was stirred at ambient temperature to obtain thick solid. The reaction mixture was heated to 60 –65°Cfor 45 to 60 minutes and the resulting the reaction mass was cooled to 0-5°C. The reaction mass was stirred at 0-5°C for the period of 1 hour and resulting solid was filtered under vacuum. Further the wet solid was dried at 60-65°C for the period of 6 to8 hours. The resulting solid was suspended in 150ml of acetonitrile and heated to reflux. 10 ml of DM water was added under reflux to obtain a clear solution. The reaction mixture was cooled to 0-5°C for 3 hours. Thus precipitated solid was filtered off and suspended in 100 ml of water. pH of the suspension was adjusted to 12 and then extracted with (3 x 100 ml) of toluene. Combined toluene layers was washed with water (2 x 50 ml), dried over anhydrous sodium sulphate, followed by distillation to afford (+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3–dihydroiso benzofuran – 5 – carbonitrile as an syrup (3.0 gm).

$[\alpha]^{25}_{D}$ = (+) 12.04° (C=1%in methanol), Chiral purity by HPLC=98.32%

Example-4

Preparation of (-) 1- (3 - aminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile: (Formula-XII)

1-(3- aminopropyl)-1-(4 -fluorophenyl)-1,3 dihydroisobenzofuran – 5 – carbonitrile (10 gm) was dissolved in 50 ml of acetonitrile. A solution of (+)-di-p-tolyltartaric acid (13 gm in 20 ml of acetonitrile) was added slowly at ambient temperature. The reaction mixture was stirred at ambient temperature to obtain thick solid. The reaction mixture was heated to 60 –65°Cfor 45 to 60 minutes and the resulting the reaction mass was cooled to 0-5°C. The reaction mass was stirred at 0-5°C for the period of 1 hour and resulting solid was filtered under vacuum. Further the wet solid was dried at 60-65°C for the period of 6 to8 hours. The resulting solid was suspended in 150ml of acetonitrile and heated to reflux. 10 ml of DM water was added under reflux to obtain a clear solution. The reaction mixture was cooled to 0-5°C for 3 hours. Thus precipitated solid was filtered off and suspended in 100 ml of water. pH of the suspension was adjusted to 12 and then extracted with (3 x 100 ml) of toluene. Combined toluene layers was washed with water (2 x 50 ml), dried over anhydrous sodium sulphate, followed by distillation to afford (-)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3–dihydroiso benzofuran – 5 – carbonitrile as an syrup (2.8 gm).

$[\propto]^{25}_{D}$ =(-)12.07°(C=1%in methanol), Chiral purity by HPLC=98.61%

Example-5

Preparation of (+) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-I)

A solution of (+) 1-(3- aminopropyl)-1-(4 -fluorophenyl)-1,3 dihydroisobenzofuran – 5 – carbonitrile (5 gm, 0.017 mole) and formaldehyde (2.5 gm, 0.084 mole, 37% aqueous solution) in 98 % formic acid (3.88 gm, 0.084 mole) was refluxed at 95 – 100°C for the 12 hours. After the solution has been cooled 5 ml of 4 N Hydrochloric acid solutions was added and resulting reaction solution is evaporated to dryness under reduced pressure. Then 1 N sodium hydroxide solution (100ml) was added to the residue and extracted with diethyl ether (3 x 100 ml). The organic extract was washed with water (2 x 100 ml), dried over anhydrous sodium sulphate and distilled off to afford the compound of the formula – I in the form of syrup (4.2 gm).

$[\alpha]^{25}_{D}$ =(+)11.26° (C=1%in methanol), Chiral purity by HPLC=97.05%

Example-6

Preparation of (-) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-V)

A solution of (-) 1-(3- aminopropyl)-1-(4 -fluorophenyl)-1,3 dihydroisobenzofuran – 5 – carbonitrile (5 gm, 0.017 mole) and formaldehyde (2.5 gm, 0.084 mole, 37% aqueous solution) in 98 % formic acid (3.88 gm, 0.084 mole) was refluxed at 95 – 100°C for the 12 hours. After the solution has been cooled 5 ml of 4 N Hydrochloric acid solutions was added and resulting reaction solution is evaporated to dryness under reduced pressure. Then 1 N sodium hydroxide

solution (100ml) was added to the residue and extracted with diethyl ether (3 x 100 ml). The organic extract was washed with water (2 x 100 ml), dried over anhydrous sodium sulphate and distilled off to afford the compound R-citalopram in the form of syrup (4.3gm).

$[\alpha]^{25}_{D}$ =(-)12.30° (C=1%in methanol), Chiral purity by HPLC=98.05%

Example-7

Preparation of 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-VIII)

A solution of 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3 dihydroiso benzofuran – 5 – carbonitrile (5 gm, 0.017 mole) and formaldehyde (2.5 gm, 0.084 mole, 37% aqueous solution) in 98 % formic acid (3.88 gm, 0.084 mole) was refluxed at 95 – 100°C for the 12 hours. After the solution has been cooled 5 ml of 4 N Hydrochloric acid solutions was added and resulting reaction solution is evaporated to dryness under reduced pressure. Then 1 N sodium hydroxide solution (100ml) was added to the residue and extracted with diethyl ether (3 x 100 ml). The organic extract was washed with water (2 x 100 ml), dried over anhydrous sodium sulphate and distilled off to afford the compound citalopram in the form of syrup (4.1 gm).

Example-8

Preparation of 1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-XIII)

10 gm of 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3 dihydroiso benzofuran – 5 – carbonitrile (0.033 mole) and benzaldehyde (4.2gm, 0.040 mole) were refluxed in a water separator for 1.5 – 2.0 hrs. in 20 ml of toluene. To the resulting solution was added 5.1 gm dimethyl sulphate (0.0405 mole) in 20 ml toluene at such a rate as to maintain reflux (15 min.). The reaction mixture was refluxed for 90 minutes, cooled and slowly treated with 30 ml water and heated to reflux for an additional 20 minutes. Cool the reaction mass and separated the aq. layer. The aq. layer was washed twice with 2 x 15 ml of diethyl ether to remove unreacted benzaldehyde and made basic pH 12 –13 with 50 % aq. NaOH. This basic aq. layer was extracted with 2 x 30 ml of diethyl ether. The organic extract was washed with water (2 x 10 ml), dried over anhydrous sodium sulphate and distilled off to afford 8 gm of the compound desmethyl citalopram in the form of syrup. The oxalate salt of the desmethyl citalopram crystallized from acetone. (8.0gm)

Example-9

Preparation of (+)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-IX)

10 gm of (+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3 dihydroiso benzofuran – 5 – carbonitrile (0.033 mole) and benzaldehyde (4.2gm, 0.040 mole) were refluxed in a water separator for 1.5 – 2.0 hrs. in 20 ml of toluene. To the resulting solution was added 5.1 gm

dimethyl sulphate (0.0405 mole) in 20 ml toluene at such a rate as to maintain reflux (15 min.). The reaction mixture was refluxed for 50 minutes, cooled and slowly treated with 30 ml water and hated for an additional 20 minutes. After cooling in ice, the aq. layer was washed twice with 2 x 15 ml of diethyl ether to remove unreacted benzaldehyde and made basic pH 12 –13 with 50 % aq. NaOH. This basic aq. layer was extracted with 2 x 30 ml of diethyl ether. The organic extract was washed with water (2 x 10 ml), dried over anhydrous sodium sulphate and distilled off to afford 7 gm of the compound (+)-desmethyl citalopram in the form of oil. The oxalate salt of the (+)-desmethyl citalopram crystallized from acetone.

$[\alpha]^{25}_{D}$ =(+)9.8° (C=1%in methanol),

Example-10

Preparation of (-)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-X)

10 gm of (-)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3 dihydroiso benzofuran – 5 – carbonitrile (0.033 mole) and benzaldehyde (4.2gm, 0.040 mole) were refluxed in a water separatior for 1.5 – 2.0 hrs. in 20 ml of toluene. To the resulting solution was added 5.1 gm dimethyl sulphate (0.0405 mole) in 20 ml toluene at such a rate as to maintain reflux (15 min.). The reaction mixture was refluxed for 50 minutes, cooled and slowly treated with 30 ml water and hated for an additional 20 minutes. After cooling in ice, the aq. layer was washed twice with 2 x 15 ml of diethyl ether to remove unreacted benzaldehyde and made basic pH 12 –13 with 50 % aq. NaOH. This basic aq. layer was extracted with 2 x 30 ml of diethyl ether. The organic extract was washed with water (2 x 10 ml), dried over anhydrous sodium sulphate and

distilled off to afford 8.2 gm of the compound (-)-desmethyl citalopram in the form of oil. The oxalate salt of the (-)-desmethyl citalopram crystallized from acetone.

Example 11 (Alternative process for the preparation of Escitalopram)

Preparation of (+) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-I)

Racemic 1-(3-dimethylaminopropyl)-1-(4-flourophenyl)-1,3dihydroisobenzo furan -5-carbonitrile (50gm), (+)-di-p-tolyltartaricacid (62gm) were suspended in 500 ml acetonitrile. The reaction mixture was stirred at ambient temperature for a period of 10-15 minutes. Further the contents were heated to 70-75°C, methanol (40.0ml) was added to the same, till a clear solution was attained. The resulting reaction mass was stirred at same temperatures for a period of 30-45 minutes. Then the reaction mass was cooled to 30 –35°C for a period of 2- 3 hours and resulting solid was filtered under vacuum. The obtained filtrate was evaporated to dryness and the resultant thick residue was suspended in aqueous sodium hydroxide solution (1.6g NaOH in 100ml Dm water). To the reaction solution toluene (100ml) was added. The reaction mixture was stirred for a period of 30-45mins, toluene layer was separated and aqueous basic solution was extracted with toluene (3 x 20ml) combined toluene layers was washed with water (3 x 20 ml), separated toluene layer followed by distillation to afford (+) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile as an thick syrup (12.0gm). Thus the obtained thick syrup was resubjected to the above process to improve the chiral purity. $[\alpha]^{25}_{D}$ =(+)10.8° (C=1%in methanol), Chiral purity by HPLC=98.89%

We Claim

1) A process for the preparation of didesmethylcitalopram (1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile which comprises;

a) heating a solution of a base selected form, LDA (lithium diisopropyl amine), NaH, n-BuLi, and metal oxides; such as NaOMe, KOMe, LiOMe, NaOtBu, KOtBu and LiOtBu preferably NaH, or KtBuO or LDA, more preferably in KtBuO in a aprotic solvent selected from the list of DMSO, THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers; such as diethyl ether, methyl tert.butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, in a anhydrous condition under nitrogen atmosphere, at a temperature of 50 – 120°C; preferably 60-65°C for more than a hour

b) cooling the reaction mixture of step (a) to temperature of 10-50°C, preferably to a temperature of 25-35°C

c) dissolving 5-cyano-1- (4-fluoro phenyl)-1,3-dihydrobenzofuran in a suitable aprotic solvent selected from the list of dimethyl sulfoxide, dimethyl formide, N-methyl pyrrolidon, ethers; such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably dimethyl sulfoxide or acetone,

more preferably the solvent is dimethyl sulfoxide, followed by its addition to the reaction mixture of step (b) at ambient temperature

d) stirring the reaction mass of step (c) for a period of 10 to 60 minutes, preferably for a period of 10-15 minutes

e) dissolving the chloropropyl amine in a aprotic solvent selected from the list of dimethyl sulfoxide, tetrahydrofuran, dimethyl formide, N-methyl pyrrolidon, ethers; such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably dimethyl sulfoxide or acetone, more preferably the solvent is dimethyl sulfoxide, followed by its addition to the reaction mixture of step (d) at ambient temperature

f) heating the reaction mass of step (e) to a temperature of 40 to 140°C for a period of 1 to 6 hrs; preferably a temperature of 40 to 45°C for 1 to 1.5 hrs

g) quenching of the reaction mass of step (f) using ice- cold water at a temperature of – 5 to 25 °C, preferably at a temperature of 0 to 5°C

h) extraction of the compound from reaction mass of step (g) with an organic solvent selected from the list of dichloromethane, chloroform, dichloroethane, toluene, xylene,

ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether, preferably toluene

i) distilling off the solvent under vacuum from the reaction solution of step (h) to get the residue

j) suspending the residue of step (i) in water followed by adjusting pH of the solution between 2 and 6 with a solution comprising hydrochloric acid, acetic acid, sulphuric acid; preferably hydrochloric acid solution followed by washing solution with a suitable organic solvent selected from class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably toluene

k) basifying the aqueous solution of step (j) to a pH of 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution

l) extracting the compound from the basified aqueous layer of step (k) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene

m) distilling the solvent from the reaction solution of step (l) to obtain a didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile) in the form of syrup

n) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile)

o) hydrolysis of the dried or wet salt of didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile) of the step (n) in water with suitable alkaline solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution

p) extracting the compound of didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile) from the solution of step (o) in a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane,

toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene

q) distilling the organic solvent of step (p) to afford the compound didesmethylcitalopram (1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile)

(2) The process for the preparation of Escitalopram,

which comprises;

a) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile

b) stirring the reaction mass of step (a) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes

c) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 – camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid,

mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (-) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures

d) adding the reaction mass of step (c) to a reaction mass of step (b) for a period of 10 to 60 minutes, preferably 10 to 15 minutes

e) heating the reaction mass of step (d) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes

f) cooling the reaction mass of step (e) a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours

g) filtering the obtained solid in step (f) followed by its washing with a solvent used in step (a)

h) drying the solid obtained in step (g) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a diastereomeric salt of compound

didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile)

i) dissolving the diastereomeric salt obtained in step (h) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably in a mixture of 15:1 acetonitrile and water combination

j) heating the reaction mass of step (i) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes

k) cooling the reaction mass of step (j) to a temperature of –20 to +30°C for a period of 1 to 72 hours; preferably –5 to 5°C for 1 to 3 hours

l) filtering the obtained solid in step (k) followed by its washing with a solvent used in step (i)

m) drying the solid obtained in step (l) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford (+)-1- (3- aminopropyl)-1-(4 - fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of (-) DPTTA salt

n) suspending the solid obtained in step (m) in water followed by adjusting the pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution

o) extracting the compound Escitalopram ((+)-1- (3- aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile) from the basified aqueous layer of step (n) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene

p) distilling the solvent from the reaction solution of step (o) to obtain (+) didesmethylcitalopram((+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3–dihydroiso benzofuran – 5 – carbonitrile)

q) reacting the compound in step (p) with suitable methylating agents such as methyl iodide , dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours , more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours

r) cooling the reaction mass of step (q) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid

s) distilling the reaction solution of step (r) to obtain a thick residue

t) suspending the residue of step (s) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide

u) extracting the compound from the basified aqueous layer of step (t) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether

v) distilling the solvent from the reaction solution of step (u) to afford Escitalopram ((+)-1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 – isobenzofurancarbonitrile)

(3) A process for the preparation of R-citalopram ((-)-1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 –isobenzofurancarbonitrile)
which comprises;

a) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform,

esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile

b) stirring the reaction mass of step (a) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes

c) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 – camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (+) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures

d) addition of reaction mass of step (c) to reaction mass of step (b) for a period of 10 to 60 minutes, preferably 10 to 15 minutes

e) heating the reaction mass of step (d) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes

f) cooling the reaction mass of step (e) to a temperature of –20 to 40°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours

g) filtering the obtained solid in step (f) followed by its washing with a solvent used in step (a)

h) drying the solid obtained in step (g) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford diastereomeric salt of compound didesmethylcitalopram (1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 –isobenzofurancarbonitrile)

i) dissolving the diastereomeric salt obtained in step (h) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures

j) heating the reaction mass of step (i) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes

k) cooling the reaction mass of step (j) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours

l) filtering the obtained solid in step (k) followed by its washing with a solvent used in step (i)

m) drying the solid obtained in step (l) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (-)-1- (3- aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of (+) DPTTA salt

n) suspending the solid obtained in step (m) in water followed by adjusting the pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution

o) extracting the compound from the basifying aqueous layer of step (n) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably toluene

p) distilling the solvent from the reaction solution of step (o) to obtain (-) didesmethylcitalopram

q) reacting the compound (-) didesmethylcitalopram ((-) 1- (3 - aminopropyl) 1-(4 - fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile) of step (p) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours , more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours

r) cooling the reaction mass of step (q) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid

s) distilling the reaction solution of step (r) to obtain a thick residue

t) suspending the residue of step (s) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide

u) extracting the compound from the basified aqueous layer of step (t) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether

v) distilling the solvent from the reaction solution of step (u) to afford (-) didesmethylcitalopram ((-)-1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 –isobenzofurancarbonitrile

(4) A process for the preparation of citalopram,

which comprises;

a) heating a solution of a base such as lithium diisopropyl amine, sodium hydride, n-butyl lithium, and metal oxides; such as sodium methoxide, potassium methoxide,lithium methoxide, sodium tertiary butoxide, potassium tertiary butoxide and lithium tertiary butoxide preferably sodium hydride or potassium tertiary butoxide or lithium diisopropyl amine, more preferably potassium tertiary butoxide in a aprotic solvent such as dimthylsulfoxide, tetrahydrofuran, dimethyl formide, N-methyl pyrrolidon, ethers; such as diethyl ether, methyl tert.butyl ether ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably dimethyl sulfoxide or acetone, more preferably the solvent is dimethyl sulfoxide, in a anhydrous condition under nitrogen atmosphere, at a temperature of 50 – 120°C; preferably 60-65°C for more than a hour

b) cooling the reaction mixture of step (a) to temperature of 10-50°C, preferably to a temperature of 30-35°C

c) dissolving 5-cyano-1- (4-fluoro phenyl)-1,3-dihydrobenzofuran in a suitable aprotic solvent such as dimethyl sulfoxide , tetrahydrofuran, dimethyl formide, N-methyl pyrrolidon, ethers; such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably dimethyl sulfoxide or acetone, more preferably the solvent is dimethyl sulfoxide, followed by its addition to the reaction mixture of step (b) at ambient temperature

d) stirring the reaction mass of step (c) for a period of 5 to 60 minutes, preferably 10-15 minutes

e) dissolving the chloropropyl amine in a aprotic solvent such as dimethyl sulfoxide , tetrahydrofuran, dimethyl formide, N-methyl pyrrolidon, ethers; such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone, more preferably the solvent is dimethyl sulfoxide, followed by its addition to the reaction mixture of step (d) at ambient temperature

f) heating the reaction mass of step (e) to a temperature of 40 – 140°C for a period of 1 to 6 hrs; preferably a temperature of 40 to 45°C for 1 to 1.5 hrs

g) quenching of the reaction mass of step (f) using ice- cold water at a temperature of – 5 to 25 °C , preferably at a temperature of 0 to 5°C

h) extraction of the compound from reaction mass of step (g) with an organic solvent selected from the list of dichloromethane, chloroform, dichloroethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether, preferably toluene

i) distilling off the solvent under vacuum from the reaction solution of step (h) to get the residue

j) suspending the residue of step (i) in water followed by adjusting pH of the solution between 2 and 6 with a solution comprising hydrochloric acid, acetic acid, sulphuric acid; preferably hydrochloric acid solution followed by washing solution with a suitable organic solvent selected from class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably toluene

k) basifying the aqueous solution of step (j) to a pH of 8 to 13 with a basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably sodium hydroxide solution

l) extracting the compound from the basified aqueous layer of step (k) with a suitable organic solvent such as dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably toluene

m) distilling the solvent from the reaction solution of step (l) to obtain didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile in the form of syrup

n) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile

o) hydrolysis of the dried or wet salt of didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile of the step (n) in water with suitable alkaline solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution

p) extracting the compound didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the solution of step (o) in a suitable organic solvent such as dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably toluene

q) distilling the organic solvent of step (p) to afford the compound didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile

r) reacting the compound didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile in step (q) with suitable methylating agents such as methyl iodide , dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours , more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours

s) cooling the reaction mass of step (r) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid

t) distilling the reaction solution of step (s) to obtain a thick residue

u) suspending the residue of step (t) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide

v) extracting the compound from the basified aqueous layer of step (u) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether

w) distilling the solvent from the reaction solution of step (v) to afford racemic 1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 –isobenzofurancarbonitrile

(5) A process for the preparation of racemic desmethylcitalopram (1-[3 – (N- methylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 –isobenzofurancarbonitrile)
which comprises;

a) dissolving the didesmethyl citalopram (1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile) in a solvent ethers; such as diethyl ether, methyl-tert-butyl ether, chloro solvents; such as dichloroethane, chloroform, dichloromethane hydrocarbons such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably the solvent is toluene

b) addition of benzaldehyde to reaction mass of step (a) to ambient temperature

c) refluxing the above reaction mass of step (b) with a water separator for a period of 2 to 10hrs at a temperature of 100-110°C preferably till the last drop of the water was collected

d) reacting the reaction mass of step (c) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1-1.5 hours

e) cooling the reaction mass of step (d) to a temperature of 90-95°C

f) treating the reaction mass of step (e) with water at a temperature at 90-95°C

g) refluxing the reaction mass of step (f) for a period of 20 –120 minutes at 90-125°C preferably 100-110°C for 30-40 minutes

h) cooling the reaction mass of step (g) to ambient temperature and followed by washing with a suitable organic solvents such as dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether

i) basifying the aqueous solution of step (h) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH of 12-13

j) extracting the compound from the basified aqueous layer of step (i) with a suitable organic solvents selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether

k) washing the organic layer of step- (j) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate

l) distilling the solvent from the reaction solution of step (k) to obtain a racemic desmethyl citalopram (1-[3 – (N- methylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 – isobenzofurancarbonitrile) in the form of thick syrup

m) the compound of step (n) is optionally purified by converting the free base into its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of desmethyl citalopram (1-[3 – (N- methylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 –isobenzofurancarbonitrile)

(6) A process for the preparation of (+) desmethylcitalopram ((+)-1-[3 – (N-methylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 –isobenzofurancarbonitrile)

which comprises;

i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile in a suitable solvent selected from the group alcohols; such as methanol, ethanol, isopropanol, butanol, ketones; such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents; such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles; such as acetonitrile, hydrocarbons; such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile

ii) stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes

iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acids; such as 10 – camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (-) di-p-toluyl tartaric acid in a suitable solvent selected from the group comprising of alcohols, such as methanol, ethanol, isopropanol, butanol or ketones; such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents; such as dichloroethane, dichloromethane, chloroform, esters; such as ethyl acetate, nitriles; such as acetonitrile,

hydrocarbons; such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures

iv) addition of reaction mass of step (iii) to reaction mass of step (ii) for a period of 5 to 60 minutes, preferably 10 to 15 minutes

v) heating the reaction mass of step (iv) to a temperature of 40 to 100°C for a period of 1 to 6 hours; preferably a temperature of 60 to 65°C for 45 to 60 minutes

vi) cooling the reaction mass of step (v) a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours

vii) filtering the obtained solid in step (vi) followed by its washing with a solvent used in step (i)

viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 to 65°C for 6 to 8 hours to afford a solid of diastereomeric salt of didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile)

ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile,

hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures

x) heating the reaction mass of step (ix) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes

xi) cooling the reaction mass of step (x) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours

xii) Filter the obtained solid in step (xi) followed by its washing with a solvent used in step (ix)

xiii) drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (+)-1- (3- aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of DPTTA salt

xiv) dissolving the solid obtained in step (xiii) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to 12-13

xv) extracting the compound from the basifying aqueous layer of step (xiv) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene,

ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably toluene

xvi) distilling the solvent from the reaction solution of step (xv) to obtain a compound of formula (+) didesmethylcitalopram ((+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile)

xvii) dissolving the (+)-didesmethyl citalopram ((+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile) of step (xvi) in a solvent selected from the list of ethers; such as diethyl ether, methyl-tert-butyl ether, chloro solvents; such as dichloroethane, chloroform, dichloromethane, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably the solvent is toluene

xviii) addition of benzaldehyde to reaction mass of step (xvii) at ambient temperatures

xix) refluxing the above reaction mass of step (xviii) with a water separator for a period of 2 to 10hrs at a temperature of 100-110°c preferably till the last drop of the water was collected

xx) reacting the reaction mass of step (xix) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1-1.5 hours

xxi) cooling the reaction mass of step (xx) to a temperature of 90-95°C

xxii) treating the reaction mass of step (xxi) with water at a temperature at 90-95°C

xxiii) refluxing the reaction mass of step (xxii) for a period of 20 –120 minutes at 90-125°C preferably 100-110°C for 30-40 minutes

xxiv) cooling the reaction mass of step (xxiii) to ambient temperature and followed by washing with a suitable organic solvents selected from the class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether

xxv) basifying the aqueous solution of step (xxiv) to a pH of 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH of 12 to 13

xxvi) extracting the compound from the basified aqueous layer of step (xxv) with a suitable organic solvent such as dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether

xxvii) washing the organic layer of step- (xxvi) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate

xxviii) distilling the solvent from the reaction solution of step (xxvii) to obtain a (+)-desmethyl citalopram ((+)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile) in the form of thick syrup

xxix) which is optionally purified by converting the free base in to its corresponding acid addition .salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of (+) – desmethylcitalopram (+)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile

(7) A process for the preparation of (-)-desmethylcitalopram ((-)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile)

which comprises;

i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile in a suitable solvent selected from group consisting of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone,

methyl isobutyl ketone, chlorosolvents; such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile

ii) Stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes

iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 – camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (+) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures

iv) addition of reaction mass of step (iii) to reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes

v) heating the reaction mass of step (iv) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes

vi) cooling the reaction mass of step (v) a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours

vii) filter the obtained solid in step (vi) followed by its washing with a solvent used in step (i)

viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a diastereomeric salt of compound didesmethylcitalopram (1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile)

ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent like water, alcohols; such as methanol, ethanol, isopropanol, butanol or ketone; such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chlorosolvents; such as dichloroethane, dichloromethane, chloroform, esters; such as ethyl acetate, nitriles; such as acetonitrile, hydrocarbons; such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures

x) heating the reaction mass of step (ix) to a temperature of 40 to 100°C for a period of 1 to 6 hours; preferably a temperature of 60 to 65°C for 45 to 60 minutes

xi) cooling the reaction mass of step (x) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours

xii) filter the obtained solid in step (xi) followed by its washing with a solvent used in step (ix)

xiii)drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (-)-1- (3- aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in the form of DPTTA salt

xiv) dissolving the solid obtained in step (xiii) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution preferably 12-13

xv) extracting the compound from the basifying aqueous layer of step (xiv) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably toluene

xvi) distilling the solvent from the reaction solution of step (xv) to obtain a compound (-) didesmethylcitalopram ((-)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile)

xvii) dissolving the (-)-didesmethyl citalopram ((-) 1- (3 - aminopropyl) 1-(4 - fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile) in a solvent selected from the group ether; such as diethyl ether, methyl-tert-butyl ether, chloro solvents; such as dichloroethane, chloroform, dichloromethane hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably the solvent is toluene

xviii) addition of benzaldehyde to reaction mass of step (xvii) at ambient temperature

xix) refluxing the above reaction mass of step (xviii) with a water separator for a period of 2 to 10hours at a temperature of 100-110°c preferably till the last drop of the water was collected

xx) reacting the reaction mass of step (xix) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1-1.5 hours

xxi) cooling the reaction mass of step (xx) to a temperature of 90-95°C

xxii) treating the reaction mass of step (xxi) with water at a temperature at 90-95°C

xxiii) refluxing the reaction mass of step (xxii) for a period of 20 –120 minutes at 90-125°C preferably 100-110°C for 30-40 minutes

xxiv) cooling the reaction mass of step (xxiii) to ambient temperature and followed by washing with a suitable organic solvents selected from the class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether

xxv) basifying the aqueous solution of step (xxiv) to a pH of 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH 12 to 13

xxvi) extracting the compound from the basified aqueous layer of step (xxv) with a suitable organic solvents selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether

xxvii) washing the organic layer of step- (xxvi) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate

xxviii) distilling the solvent from the reaction solution of step (xxvii) to obtain a (-)-desmethyl citalopram ((-)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile) in the form of thick syrup

xxix) the compound of step (xxviii) is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chlorosolvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of (-) desmethylcitalopram (-)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile

(8) A process for the preparation of Escitalopram from citalopram and its pharmaceutically acceptable salts

which comprises:

(i) converting any salt of racemic citalopram into its free base with a inorganic base selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate in a suitable organic solvent

ii) separating the organic layer of step (i) followed by concentrating the obtained layer to afford the residual mass

iii) converting the free base obtained in step (ii) in to diastereomeric salts with an optically active acid such as tartaric acid, di-p-toluyl tartaric acid, camphorsulphonic acid, malic acid, N-acetyl glutamic acid or mandelic acid, in a suitable solvent selected from alcohols, sucha as methanol, ethanol, isopropanol, butanol, chlorosolovents such as Dichloromethane, dichloroethane, chloroform, nitriles such as, acetonitrile,

hydrocarbons such as toluene, xylene, cyclohexane, heptane, esters, such as ethyl acetate, ethers such as diethyl ether, diisopropylether, methyl tert-butyl ether, ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and mixtures thereof, preferably chiral acid is di-p-toluyl tartaric acid and the solvent is mixture of acetonitrile and methanol

iv) filtering the solid obtained in step (iii) and concentrating the mother liquor to thick residue

v) the residue obtained in step (iv) is converted in to free base and repeated the steps (i) to (iv) to obtain the di-p-toluyl tartaric acid salt of escitalopram

vi) hydrolyzing the salt obtained in step (v) using inorganic base selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate in a suitable organic solvent selected from water immiscible solvents such as, chloroform, dichloromethane, dichloroethane, toluene, ethyl acetate, diethyl ether, diisopropylether, methyl tert-butyl ether preferably the base is sodium hydroxide and solvent is toluene

vii) evoparating the solvent of step (vi) under reduced pressure to afford escitalopram ((+) 1-(3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile) as an oil which is further optionally converted to its pharmaceutically acceptable salts.

(9) A process according to claims 2 and 8 the particle size of Escitalopram ((+) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile) and its pharmaceutically acceptable salts is 1 to 150 microns.

Dated: 13th day of April 2004

(Signed) S. Venkataraman

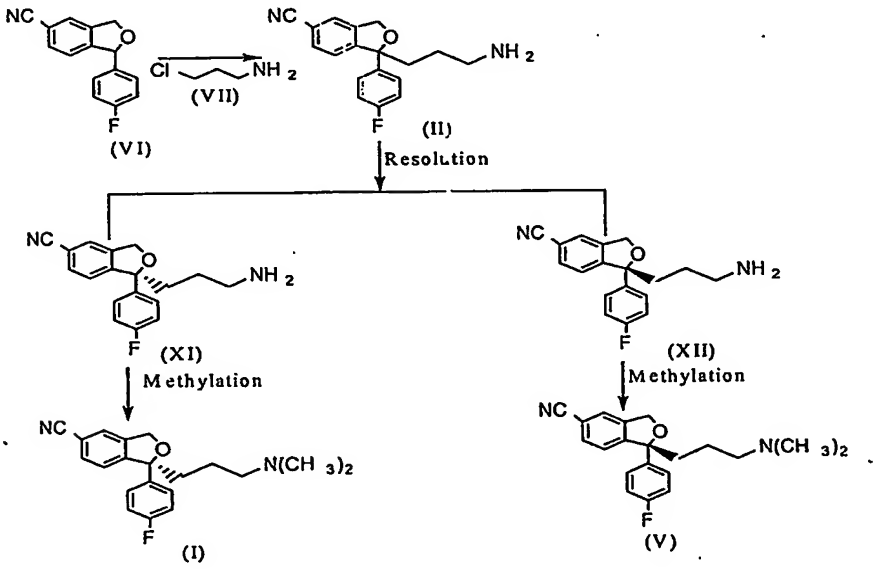
Sundaram Venkataraman,
Vice-President (R&D),
Dr.Redddy's Laboratoties Limited

ABSTRACT

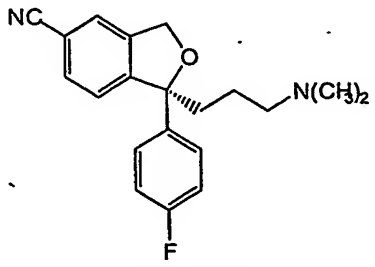
Title of the invention: "A novel process for the preparation of (+)-1-(3-dimethylaminopropyl)-1-(4-flourophenyl)-1,3-dihydrobenzofuran-5-carbonitrile (Escitalopram) and pharmaceutically acceptable salts thereof".

The present invention provides a novel process for the preparation of Escitalopram and pharmaceutically acceptable salts.

A process for the preparation of Escitalopram of the present invention comprises, condensation of isobenzofuran of Formula (VI) with chloropropyl amine of Formula (VII) to afford a compound of Formula (II), which is further subjected to resolution followed by methylation to afford compound of Formula-I as mentioned in Scheme -I.



Escitalopram can be shown as Formula (I)



Formula (I)